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HEREDITARY ANGIOEDEMA WITH C1 ESTERASE INHIBITOR DEFICIENCY: THE IMPORTANCE OF APPROPRIATE TREATMENT - CASE REPORT

Sales José Lopes Gonçalves Rosa
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0001-6120-4611

Luisa Miranda Zafalão
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0003-3284-9490

Danielly Christine Vargas de Espindula Leite
Universidade Federal de Jataí (UFJ)
Jataí - GO
http://lattes.cnpq.br/3377913013856932

Monique Costa Dias
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0002-9521-062X

Arícia Mota
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0001-6254-583X

Júlia Pires de Farias
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0002-1176-6349

Marcela Costa de Almeida Silva
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0001-5211-055X

André Gebrim Matias
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0002-3351-1005

Sara Alves França
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0002-8382-1394

Ana Elisa Pereira Braga
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0002-9998-485X

Arthur Victor Vilela Barros
Universidade Federal de Jataí (UFJ)
Jataí - GO
https://orcid.org/0000-0002-9266-5549

Fábio Morato de Oliveira
Universidade Federal de Jataí (UFJ)
Jataí - GO
http://lattes.cnpq.br/6212902574295781

Abstract: Hereditary Angioedema with C1 esterase inhibitor deficiency (HAE-C1-INH) is a rare condition, genetic in nature, autosomal dominant, caused by a mutation in the SERPING1 gene, altering the C1-INH protein. It is characterized by recurrent edema in the subcutaneous and submucosal tissues. It is underdiagnosed due to the non-specificity of symptoms and low incidence. There are several forms of HAE, characterized by the number and function of C1-INH. As a differential diagnosis, there is angioedema due to the use of ACE inhibitors and acquired angioedema. Treatment aims to control acute crises and carry out short and long-term prophylaxis, involving medications and non-pharmacological measures. This is a case report of Hereditary Angioedema with C1 esterase inhibitor deficiency (HAE-C1-INH). Data were collected after the patient's consent, including laboratory test results. The clinical discussion is based on 14 articles selected from the PMC, Scielo and Up to date databases, excluding studies not aligned with the objective and/or prior to 2018. The study is descriptive and exploratory, highlighting characteristics, clinical repercussions, diagnosis and treatment of the HAE-C1-INH. This study presents a case of a female patient, 42 years old, with HAE-C1-INH and Borderline Personality Disorder. The patient had recurrent episodes of edema since childhood, with multiple hospital admissions. The diagnosis was established after years of ineffective treatment for allergic reactions. His family history revealed several affected members. The patient's treatment involves the chronic use of specific medications, with a significant improvement in quality of life and a reduction in episodes of edema. The importance of early diagnostic investigation and appropriate treatment is highlighted to improve the quality of life and prognosis of HAE-C1-INH. The specific therapeutic

approach allowed the patient to lead a healthy life, with few episodes of edema and without the need for hospitalization or drastic interventions.

Keywords: Hereditary Angioedemas; Angioedema; Complement Inhibitor Protein C1; Hereditary Complement Deficiency Diseases.

INTRODUCTION

Hereditary Angioedema with C1 esterase inhibitor deficiency (HAE-C1-INH) is a rare disease, of autosomal dominant genetic origin, which affects subcutaneous and submucosal tissues, causing recurrent edema. The condition occurs due to quantitative and/or functional deficiencies of the C1 esterase inhibitor (C1-INH), triggered by a mutation in the SERPING1 gene, which is responsible for coding this protein. Family history reinforces diagnostic suspicion, since 70 to 80% of cases occur in family members and approximately 25% of cases occur due to new spontaneous mutations (KURK, T. et al., 2020).

Identification of the disease is a challenge because it presents differential diagnoses, such as: angioedema due to the use of ACE inhibitors, acquired angioedema, among others. In addition, it can be classified into different forms: HAE type 1, HAE type 2 and HAE with normal C-INH. Each subtype differs from each other due to quantitative and functional aspects of C1-INH, consequently presenting different clinical manifestations and treatments (ZAFRA, H. 2022).

Due to the non-specificity of symptoms and low incidence of the disease (initially estimated at 1:10,000 to 1:50,000), the comorbidity is underdiagnosed and inadequately treated, leading to frequent visits to emergency units, admissions to wards and intensive care units. It is estimated that the mortality rate for patients with the most severe form of the disease (laryngeal angioedema), without treatment, is between 25 and 40% (GIAVINA-BIANCHI, P. et al., 2022).

The treatment of HAE-C1-INH is based on the treatment of acute crises and short- and long-term prophylaxis, including the use of drugs and non-pharmacological measures, such as identifying and avoiding triggering factors. In general, drugs for acute crises are authorized for self-administration (CABALLERO, T. 2021).

Therefore, this study, through a case report, aims to highlight the importance of diagnostic investigation and appropriate treatment to guarantee quality of life and a better prognosis of the disease.

METHODOLOGY

This is a case report conducted from a qualitative approach and classified as a descriptive and exploratory study (PEREIRA et al., 2018), which investigates the characteristics, clinical repercussions, diagnosis and treatment of a typical case of Hereditary Angioedema with C1 esterase inhibitor deficiency (HAE-C1-INH).

The data used in this case report were obtained and shared only after the patient read, agreed and signed the Informed Consent Form (TCLE). After authorization from the patient, she collaborated by providing the results of the laboratory tests performed and relevant information related to her case.

The discussion of the clinical case was based on articles selected from the PubMed Central (PMC), Scielo and Up to date databases. On the PMC platform, a search was carried out using the descriptors "Hereditary Angioedema" and applying the filters: "in the last 5 years", "Free full text", "English" and "Portuguese", which resulted in the identification of 561 studies. In the Scielo database, 23 articles were identified using the same descriptors as in the PMC database, with the filters: "All collections; all languages; Health Sciences; last 5 years".

Finally, an extensive search was also carried out on Up to date, using the same descriptors as the other scientific bases.

The identified articles were subjected to an analysis of scientific evidence and their relationship with the objective of this study. Articles that did not meet the proposal were discarded, in addition to those published before 2018 and duplicates. Therefore, 07 articles were selected from the database PMC, 04 from the Scielo database and 03 from Uptodate, totaling 14 articles.

CLINICAL CASE

IDENTIFICATION

This is a female patient, single, 42 years old, self-identified as mixed race, retired due to permanent disability for 2 years and carrier of HAE-C1-INH and Borderline Personality Disorder (BPD). Due to this clinical situation, the patient uses 150 mg of Bupropion Hydrochloride daily in the morning and afternoon, in addition to 25 mg of Topiramate at night and three weekly applications of Berinert® (C1 esterase inhibitor derived from human plasma). During exacerbations of the HAE-C1-INH condition, the patient uses Firazyr® applications (bradykinin receptor antagonist). She denies allergies and has already had surgery on her right foot for a fracture unrelated to HAE-C1-INH.

The patient was the first member of her family to be diagnosed with this condition. After confirmation, her family members were encouraged to investigate as it is an autosomal dominant genetic disease. As a result, several cases were discovered within the family. In the Heredogram created (Figure 01), it can be seen that a grandfather, three uncles, two cousins, three cousins, his mother and his brother have the same diagnosis. In addition to HAE-C1-INH, the patient's family history includes Systemic Lupus Erythematosus (SLE) in her mother and grandmother.

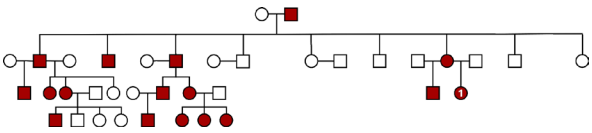

Figure 01: Graphic representation by pedigree of the relationships between the individual (1) and their family members with Hereditary Angioedema.

The patient, who lives alone and has no children, adopts balanced lifestyle habits, with a balanced diet and daily physical activity. Denies smoking, drinking alcohol or using any illicit substance. Although she sleeps around 8 hours a day, she reports that her sleep is not restful.

CLINICAL HISTORY

As a carrier of HAE-C1-INH, the patient lived throughout her life with recurrent episodes of edema in different parts of her body and multiple hospital admissions. The first episode of edema presented by the patient was at 6 months of age, with intense swelling in the hands. After that, she spent her childhood living with this condition and, at the age of 9, required, for the first time, hospitalization due to pulmonary edema (which, today, is suspected to have been a manifestation of HAE-C1- INH).

When the patient presented edema, it mainly affected the face, abdominal region and feet, sometimes associated with temporary loss of vision, abdominal pain, fecal incontinence and anorexia. The condition, without treatment, took around 15 days to resolve spontaneously.

With evidence of edema, the patient sought care in emergency units, where she was frequently diagnosed with allergic reaction attacks, receiving treatments based on the use of antihistamines, epinephrine and glucocorticoids, drugs known to be ineffective

for HAE-C1-INH. As the cases of supposed allergic attacks were recurrent, the patient underwent a total of 62 allergy tests in 2010 and all came back with negative results.

In 2014, the patient presented with glottis edema and needed to be admitted to the intensive care unit (ICU) for 3 days, requiring an advanced airway through orotracheal intubation (IOT). During this hospitalization, the possibility of his diagnosis being hereditary angioedema was raised. After discharge from hospital, the patient was evaluated by a doctor specializing in allergy and immunology, where the diagnosis of HAE-C1-INH was finally obtained. After this condition, in 2016, the patient presented another episode of glottis edema, requiring ICU, OTI and blood plasma transfusion to reverse the condition. Later that year, she underwent new tests (Table 01) that corroborated the already established diagnosis of HAE-C1-INH.

EXAMS	RESULTS	VALUES OF REFERENCE
C1 S Esterase Functional Inhibitor (qualitative)	< 0.1%	80 to 130%
C1 Esterase Inhibitor	2 mg/dL	21 to 39 mg/dL
C4 serum complement	8 mg/dL	12 to 36 mg/dL

Table 01: Exams performed by the patient on October 6, 2016

TREATMENT IMPLEMENTED

From November 2016, the patient began a therapeutic approach with specific medications for HAE-C1-INH, with applications of Firazyr® (icantibant acetate) at the beginning of acute crises (in general, she used it around 4 times a month). From 2021 onwards, prophylactic treatment with Berinert® (nanofiltered and purified C1-INH concentrate derived from human plasma) was implemented, in 03 weekly doses, and has been used to date. With the start of short-term prophylactic treatment and the treatment of symptomatic acute crises, there was no need for further ICU admissions, interventions such as OTI or even hospital admissions for the condition.

The two medications for chronic home use for HAE-C1-INH mentioned are considered high-cost and financially unviable for the vast majority of people. According to the patient in this report, she has the opportunity to obtain the drugs for free, provided by the state, via the SUS (Unified Health System).

Since the beginning of treatment, the patient has led a healthy life with few episodes of edema, which are quickly reversed with the application of emergency medication. She underwent new laboratory tests in February 2022 (Table 02), which showed the presence of the condition, although the current clinical picture and quality of life are much more positive compared to the period in which she was not receiving adequate treatment.

EXAMS	RESULTS	REFERENCE VALUES
C1 S Esterase Functional Inhibitor (qualitative)	2.5%	80 to 130%
C1 Esterase Inhibitor	2.9 mg/dL	21 to 39 mg/dL
C4 serum complement	1 mg/dL	12 to 36 mg/dL

Table 02: Exams performed by the patient on February 24, 2022

RESULTS AND DISCUSSION

DEFINITION

Hereditary Angioedema with C1 esterase inhibitor deficiency (HAE-C1-INH) is a rare disease, inherited in an autosomal dominant manner, which affects subcutaneous and submucosal tissues, causing recurrent edema, due to a mutation in the SERPING1 gene, responsible for coding the C1-INH protein. A positive family history reinforces diagnostic suspicion, since 70 to 80% of cases occur in family members and approximately 25% of cases occur due to new spontaneous mutations (KURK, T. et al., 2020).

PATHOPHYSIOLOGY

HAE is a condition resulting from the deficiency of the C1 inhibitory protein (C1-INH), produced by the liver, which has the function of inhibiting the complement system (CS) by inhibiting the initial activation complex of the first component of the classical pathway. of the SC. At low or dysfunctional levels, unregulated SC activity is allowed, which leads to vascular permeability and edema (SINNATHAMBY E. et al., 2023). Furthermore, this protein acts to control the activation of other complement pathways, such as the alternative pathway and the lecithin pathway (CAMPOS, R. et al., 2021).

In addition, C1-INH also regulates factor XII and kallikrein, controlling the activation of the contact system and, consequently, the formation of bradykinin. The action of the contact system begins with the activation of factor XII, which induces the generation of kallikrein from a serum precursor. In turn, kallikrein cleaves high molecular weight kininogen, forming bradykinin, which acts on the B2 receptors of endothelial cells, increasing vascularization (CAMPOS R. et al., 2021) (SINNATHAMBY E. et al., 2023).

Furthermore, C1-INH controls the fibrinolytic system, which promotes the activation of plasminogen with generation of plasmin, responsible for the degradation of fibrin. Thus, C1-INH acts as an antifibrinolytic (CAMPOS, R. et al., 2021).

The contact, coagulation, complement and fibrinolysis systems interact with each other. This way, greater activation of these systems in the HAE-C1-INH results in greater formation of bradykinin, in addition to a reduction in the serum C4 fraction of SC (SINNATHAMBY E. et al., 2023), resulting in greater endothelial permeability and vascularization, and promoting generalized edema and erythema characteristic of HAE-C1 -INH.

The extensive pathophysiology of HAE-C1-INH mediated by bradykinin justifies the refractoriness of typical drugs for treating allergic attacks and anaphylactic reactions, such as, for example, glucocorticoids, epinephrine and antihistamines (ZURAW, B.; FARKAS, H., 2023). The use of these drugs with little or no scientific robustness for the condition reinforces the need to expand medical knowledge about the pathology and its specific and efficient treatment.

SIGNS AND SYMPTOMS

The symptoms of HAE-C1-INH usually begin in childhood or puberty, causing swelling of the subcutaneous and submucosal tissues, especially in the cutaneous, gastrointestinal and respiratory systems (RADOJICIC, 2022). Gastrointestinal symptoms can be confused with acute abdominal symptoms, making diagnosis difficult. Respiratory system involvement can be serious and potentially fatal if it affects the larynx, triggering glottis edema that leads to hypoxia. (SCHMAIER, A. et al., 2019).

In crises, pain, nausea, vomiting, diarrhea and airway obstruction are often present. Furthermore, there may be the appearance of prodromal signs and symptoms, such as erythema marginatum, in which there is the appearance of erythematous lesions that are not accompanied by itching (ZEFRA, 2022). The presence of a non-pruritic erythematous rash is an important symptom to differentiate HAE from other types of angioedema. After the appearance of the prodrome, the crisis progresses in severity for 24 hours and usually ends within 2 to 3 days. Furthermore, it is worth highlighting that one system is affected at a time in each crisis.

Involvement of the respiratory system has a greater potential for severity, especially when there is involvement of the upper airways, such as laryngeal edema, which can lead to

hypoxia (ZURAW, B.; FARKAS, H., 2020). In children, laryngeal edema is rare, however, when it occurs, asphyxia, it develops more quickly than in adults, due to the smaller diameter of the airways (CAMPOS R. et al., 2021). The patient in this case report was an example of the important severity of crises that occur with laryngeal edema, given the need for three orotracheal intubations to maintain the patency of her airway.

Skin crises are the most common and involve swelling, redness and pain in different areas of the body, mainly extremities, face and genitalia. This symptom begins with a tingling sensation and skin irritation, progressing over a few hours to a feeling of tightness. The resolution of the edema corresponds to the duration of the crisis, which can be 2 to 3 days (ZURAW, B.; FARKAS, H., 2020). This was the initial clinical picture, still as an infant, of the patient in the present study.

The involvement of the gastrointestinal system is accompanied by cramps, nausea, vomiting and diarrhea, which results from edema of the intestinal mucosa. Intense abdominal pain can simulate acute abdominal pain, which may lead to unnecessary surgical interventions.

DIAGNOSIS

To diagnose HAE, it is necessary to obtain a detailed clinical history, associated with a physical examination and response to conventional treatments with antihistamines and corticosteroids. In HAE, a family history of angioedema, in addition to persistent edema for 3 to 5 days and the lack of response to conventional treatment, corroborate the suspicion.

HAE is classified as type I, when there is a deficiency in the concentration of the C1 esterase inhibitor, type II, when despite the concentration being normal, there is dysfunction of the C1 inhibitor, and type III, in which the C1 inhibitor is normal, but presents mutations in other genes or has an unknown cause (SCHMAIER, A. et al., 2019).

The laboratory diagnosis of HAE is made by measuring complement C4, followed by evaluating the level of C1-INH protein. Assessment of C1-INH functionality is made when the concentration of this protein is normal or elevated. In type I HAE, C4 levels are often low, as are C1-INH levels and functionality. In HAE type II, the C4 dosage and C1-INH functionality are low, but the dosage of C1-INH is normal or even elevated. In HAE type III, the levels of complement system factors are normal, varying according to the genetic mutation.

After a diagnosis of HAE has been established, it is recommended that individuals with a positive family history be considered at risk and investigated, even if asymptomatic (LÓPEZ, A. et al, 2021). The main differential diagnoses include other causes of angioedema, such as ACEi-triggered angioedema, acquired angioedema and idiopathic angioedema (ZAFRA, H. 2022).

With the results of laboratory tests (Table 01 and Table 02), positive family history, suggestive clinical history and documented inefficiency of typical interventions for allergic crises, the study patient was diagnosed with Hereditary Angioedema with C1 esterase inhibitor deficiency (HAE-C1- INH).

RECOMMENDED DRUG TREATMENT

Patients with HAE must, first of all, avoid using medications that contain estrogen and/or ACEi, due to the potential worsening of the condition when associated with these medications. The basis of pharmacological treatment for HAE aims to reduce the morbidity and mortality of the disease and improve patients' quality of life, and consists of three pillars: controlling angioedema crises;

prevent new crises during risk situations; and prevent the emergence of new crises (CABALLERO, T. 2021).

Currently, drug treatment for HAE is based on 4 specific medications, which are: intravenous (IV) pdC1INH (nanofiltered and purified C1-INH concentrate derived from human plasma); rhC1INH IV (recombinant human C1-INH); subcutaneous (SC) icantibant acetate and ecalantide. There are two types of pdC1INH marketed worldwide, Berinert® (from CSL-Behring), which is effective, safe and approved by the FDA (United States Food and Drugs Administration), and Cinryze® (from Takeda Pharmaceutical Company Ltd), effective and safe, approved by the EMA (European Medicines Agency). Icantibant acetate (Firazyr®, from Takeda Pharmaceutical Company Ltd) is a safe and effective medicine, approved by the FDA and EMA. rhC1INH (Ruconest, Pharming Group NV) is produced using transgenic rabbits and approved by the EMA and the FDA. Finally, ecalantide (Kalbitor®, from Takeda Pharmaceutical Company Ltd) is effective in acute crises, approved by the FDA (CABALLERO, T. 2021) (MAURER, M. et al., 2022).

After diagnosing the disease, it is recommended that people with HAE have medications at home and are adequately trained so that they or their family members can self-medicate during angioedema attacks. Ecalantide is the only one of the 4 medications that cannot be administered at home due to its risk of triggering anaphylactic reactions, therefore, it must be administered in a hospital environment (CABALLERO, T. 2021).

For the treatment of angioedema crises, pdC1INH, rhC1INH and ecalantide must be used, aiming to treat early to reduce morbidity and mortality (CABALLERO, T. 2021). Angioedema attacks that affect the upper airways must be considered medical emergencies and treated immediately (SERPA, F. et al., 2021) (ZURAW, B.; FARKAS, H., 2023).

In addition to standard HAE treatment, there are short- and long-term prophylaxis. Short-term prophylaxis (PCP) is indicated on occasions such as: pre-medical or dental procedures, pre-surgery, travel, special occasions (weddings, exams...), periods of stress (divorce, evaluations...), or even triggers that are known to the patient. Therapy aims to prevent angioedema attacks. The medications of choice are Berinert® or Cinryze® (ZURAW, B.; FARKAS, H., 2023). Long-term prophylaxis (PLP), or routine prophylaxis, is the maintenance treatment of HAE, aiming to reduce the frequency, severity and duration of attacks. PLP is instituted when the disease is not adequately controlled with on-demand therapy and takes into consideration, disease activity and HRQoL (health-related quality of life), and can even be applied when the patient faces some period of life associated with an increase in the disease (CABALLERO T., 2021) (ZURAW, B.; FARKAS, H., 2020).

All indications and treatment recommendations described in this article were based on the World Allergy international guidelines.

The Organization and the European Academy of Allergology and Clinical Immunology (WAO/EAACI), and take into consideration, the safety levels and degrees of recommendation and evidence of the guidelines described (CABALLERO T., 2021) (MAURER, M. et al., 2022).

FINAL CONSIDERATIONS

Experience with this approach highlights the need for early diagnosis to ensure a better quality of life and prevent fatal outcomes for severe cases of HAE-C1-INH. During the entire period in which the patient was underdiagnosed and under inefficient medical interventions for her condition, she suffered significant risks to her life, requiring multiple admissions to an intensive care bed and obtaining an advanced airway on three occasions due to edema of the glottis.

The article in question elucidates the importance of disseminating adequate scientific information so that medical staff are able to suspect this rare and potentially fatal condition in serious cases. After making the diagnosis, rapid intervention is necessary, including both the implementation of short- and long-term prophylaxis, as well as rescue treatment for acute symptomatic crises. This therapeutic approach has robust support from scientific literature in preserving lives and improving the general prognosis of HAE-C1-INH patients.

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